UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/284,100	04/07/99	NARHI L	A-423C

HM12/0814

021069
AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

EXAMINER	
PRASAD,S	

ART UNIT	PAPER NUMBER
1646	12

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev.11/00)

Office Action Summary	Application No. 09/284,100	Applicant(s) Narhi et al.	
	Examiner Sarada C Prasad	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8,10-22,25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8,10-22,25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

1. Receipt of Applicants' arguments and amendments filed in Paper No. 10 (6/8/01) is acknowledged. Amendments to claims 13-16, 18, 21-22 and 25 and new claims 26-27 have been entered. Currently, original claims 11-12, 17, 19-20 amended claims 25, 6-8, 10, 13-16, 18, 21-22; and new claims 26-27 (Paper No.10, 6/8//01) are under consideration.

2. Receipt of IDS (6/12/01) with listing of references is also acknowledged.

3. The following previous rejections and objections are withdrawn in light of Applicants' amendments filed in Paper No. 10, 6/8/01.

(i) the rejection of claims 6-8, 10-22, and 25 under 35 U.S.C. 112, second paragraph-as being indefinite;

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections to claims:

5. Claim 25 is objected to because it is not sequence compliant in reciting the polypeptide of the invention in the form of a sequence representing amino acids with the three letter code. Each polypeptide or polynucleotide should be recited with a corresponding SEQ ID NO.

Claim Rejections - 35 USC § 112 first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 25, 6-8, 10-22, 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of variants that are truncated forms of KGF-2 for example, dN29 gFGF10, dN20 hFGF10 of KGF-2, does not reasonably provide enablement for 'any other variants' that could be used as pharmaceutical compositions for treatment of diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6a. Claim 25 reciting 'a variant of KGF-2....' is overly broad. Instant specification sets forth KGF-2 polypeptide of SEQ ID No. 2 and its two variants dN29 gFGF10, dN20 hFGF10 (example 1, page 73, 1st paragraph). However, the claim language can be interpreted to mean several variants, particularly the truncated forms. There is no guidance provided in the specification for screening such undefined variants of KGF-2 without delimiters. Each variant has to be described with the entire sequence and its biological properties similar or dissimilar to KGF-2. Predictability in the art would suggest that several variants claimed would result from obvious analogous substitutions to KGF-2 at neutral positions with equivalent amino acids and provide polypeptides very similar to that of instant SEQ ID No.2, while others may exhibit no structural or functional similarity to KGF-2 and of any value in being able to replace the function of KGF-2. It is not possible to one of skill in the art to practice the instant claims where one would have to perform undue experimentation to test each substitution and find out the functionality of the resulting KGF-2 like polypeptides.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue (In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404).

Therefore, considering the breadth of claim 25, state-of-the-art, guidance provided in the specification, the amount of experimentation required is undue to practice the invention as claimed.

Claims 6-8, 10-22, 26-27 are rejected insofar as they depend on claim 25.

6b. Claims 20-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims 20-22 recite 'A pharmaceutical composition comprising a variant of KGF-2.....'. The claim language encompasses that the composition can be used for treatment because pharmaceutical composition connotes substances intended for therapeutic use. Specification provides support to prepare two different truncated polypeptides of KGF-2, however no description is provided to use them particularly for any diseases. The specification discloses that the KGF-2 polypeptides may retain some or all of the biological activity of KGF-2 (page 3, summary, 1st para) and KGF-2 variants as polypeptides that have properties of 'desired use' (detailed description, page 6, 3rd para). Such description is not commnsurate with enabling description that the Applicants are in fact in possession of the invention as pharmaceutical compositions.

The specification is non-enabling for a pharmaceutical composition that could be used for treatment, for example: injury of bone or cartilage and as a wound healing promoter. General intended use does not provide sufficient support for enablemnet of use. Furthermore, there is no actual reduction to practice of the claimed invention, or administration of the variant KGF-2

polypeptides for treatment purposes or measurement/detection of expected outcomes of ailments, or recognition of criteria of relief of the symptoms of disease. Applicants must convey with reasonable clarity, to those skilled in the art, as of the filing date sought, he or she was in possession of the invention. Therefore, knowledge of the polypeptide variants of KGF-2 does not allow one skilled in the art to envision and make and use the polypeptide of the instant invention. Conception of the claimed invention can not be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the potential methods for expressing the protein, by recombinant methods. Therefore the Applicants have not provided sufficient evidence that they were in possession of the invention at the time of filing as it is claimed and thus written description requirement has not been satisfied for the claims as they are recited. Applicant's attention is drawn to Guidelines for the examination of patent Applicants under 35 U.S.C. 112 first paragraph, "Written Description" requirement, federal register, Vol.66, No. pages 1099-111, Friday January, 2001.

Claims 6-8, 10-22, 26-27 are rejected insofar as they depend on claim 25.

Claim Rejections - 35 USC § 112-second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25, 6-8, 10-22, 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7a. Claim 25 recites polypeptide sequence with three letter amino acid code and residues 71-208 in parenthesis. The use of such parenthesis is confusing because the same type of parenthesis is used to indicate deleted words or phrases while amending the claims. This rejection can be obviated by reciting the variable portion of the sequence with delimiters.

7b. Claim 25 recites the truncated form of KGF-2 represented by SEQ ID No.2 by three letter amino acid code. This rejection can be obviated by reciting the instant sequence represented in more conventional forms such as residue x1 to residue xN of SEQ ID No. 2.

Claims 6-8, 10-22, 26-27 are rejected insofar as they depend on claim 25.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8a. Claims 25, 10-16, 18-19, 26-27 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 9625422 A (Aug 1996).

WO 9625422 A teaches fragments, derivative or analog of the polypeptide of SEQ ID No. 2 (page 9, entire 3rd para, and Example 2), which meets the limitations of the instant

claims 25 reciting the KGF-2 polypeptide with an N-terminal truncation, thus anticipating instant claims 25, 10-16, 18-19, 26-27.

8b. Claim 25, 10-16, 18-19, 26-27 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/11951 (April 1996).

WO 96/11951 teaches a number of analogues of KGF (closely related to KGF-2) suggested to be more stable than the parent molecule (page 39-claims 1-15; page 25-Example 1), thus anticipating variants of KGF-2 as claimed in the instant claims 25, 10-16, 18-19, 26-27.

8c. Claims 25, 10-16, 18-19, 26-27 are rejected under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 5,863,767 (1999).

U.S. Patent No. 5,863,767 teaches KGF $_{des}$1-23 or an analogue thereof that is composed of a portion of an amino acid sequence of mature full-length KGF (abstract line 1-3). U.S. Patent No. 5,863,767 also teaches a DNA molecule encoding the said fragment, an expression vector, and a transformed host containing the DNA molecule, a method of producing KGF $_{des}$ 1-23 by culturing the transformed host (abstract, lines 9-end) thus anticipating instant claims 25, 10-16, 18-20, 26-27.

Disclosure of U.S. Patent No. 5,863,767 also teaches therapeutic compositions containing KGF $_{des}$ 1-23 in a pharmaceutical carrier to be used for healing purposes (abstract, last two lines) thus anticipating instant claims 20-22.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9a. Claims 25, 10-16, 18-19, 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO9720929-A1 (6/1997), in view of U.S. Patent No. 5,863,767 (1999).

WO9720929-A1 teaches recombinant fibroblast growth factor FGF-10, corresponding to the entire length of SEQ ID No. 2, and related DNA, vectors containing the DNA, host cells containing the vectors, transformant host cells (pref. E.coli, or an animal cell such as COS CHO, NSO containing the vectors) (translation of the Derwent abstract, lines 1-7) (see attached sequence comparison). N-terminal truncations of KGF-2 polypeptides are well known to be more active forms of these proteins in the art thus anticipating instant claims 25, 10-16, 18-19, 26-27. However, it is not clear due to the nonavailability of translation of this document if WO9720929-A1 taught N-terminal truncation of KGF-2 to achieve polypeptides with enhanced biological activities.

U.S. Patent No. 5,863,767 (1999) teaches that truncated forms of KGF-2 possess enhanced biological activity (title itself). Teachings of U.S. Patent No. 5,863,767 (1999) have

been set forth above in paragraph 8c. Therefore it would have been obvious to one of skill in the art to have combined the teachings of WO9720929-A1 (6/1997) to use the KGF-2 polypeptide and those of U.S. Patent No. 5,863,767 to obtained N-terminally truncated forms that possess enhanced biologically activity. The motivation is provided by the need to administer lower the amounts of the kGF-2 polypeptides required to administer for treatment purposes thus making claims 25, 10-16, 18-19, 26-27 obvious.

9b. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO9720929-A1 (6/1997) in view of U.S. Patent No. 5,863,767 (1999) as applied to claims 25, 10-16, 18-19, 26-27 above, and further in view of McGwire et al. (1996).

Teachings of U.S. Patent No. 5,863,767 (1999) have been set forth above in paragraph 8c. U.S. Patent No. 5,863,767 (1999) also teaches that truncated forms of KGF-2 possess enhanced biological activity (title itself). However, U.S. Patent No. 5,863,767 did not teach other modifications of the variant KGF-2 polypeptides that can enhance the stability of KGF-2. McGwire et al. teaches effects of N-glycosylation, N-terminal cleavage on intracellular stability (title of the citation). Posttranslational modifications of gp63, in particular N-glycosylation of it, contributed to intracellular stability of gp63 (abstract, lines 26-29). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of U.S. Patent No. 5,863,767 (1999) to generate truncated forms of KGF-2 and those of McGwire et al. (1996) to N-glycosylate the truncated KGF-2 polypeptides to enhance their stability even further. Additional modifications to generate KGF-2 variants, such as chemical derivatives, to further enhance solubility properties, comprising water-soluble polymer conjugated to variant of KGF-2

would also have been obvious to one of skill in the art. The motivation is provided by the need to have stable forms of KGF-2 with enhanced biological activity for both in vitro and in vivo use.

Conclusion

10. No claims are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
August 10th , 2001

Yvonne Eyler
YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600